Kidney International (2008) **74,** 139–140. doi:10.1038/ki.2008.254

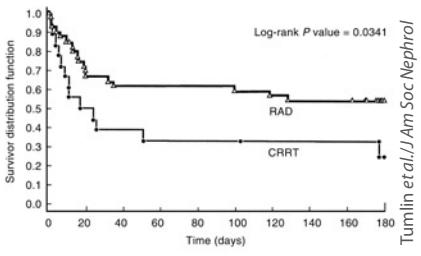
New renal tubule cell therapy is found safe and lowers death rates in patients with acute renal failure

A prospective trial conducted at 12 clinical centers in the United States evaluates the impact of the renal tubular assist device (RAD) on all-cause mortality at 28 days among patients with acute renal failure. The RAD (RenaMed Biologics) is an extracorporeal circuit fabricated with a standard hemofiltration cartridge containing nonautologous human renal tubular cells grown along the inner surface of the hollow fibers and is incorporated in series with a separate hemofiltration cartridge. Animal studies of this device demonstrate that the cells retain transport, metabolic, and endocrine activities. Further, the two-cartridge system was found to replace filtration, transport, metabolic, and endocrine function in acutely uremic animals and to lessen multiorgan dysfunction in Gram-negative sepsis in large animals.

Tumlin *et al.* randomized 58 patients, 40 to the RAD and 18 to continuous renal replacement therapy (CRRT) alone. Eligible patients required CRRT for the treatment of acute renal failure due to acute tubular necrosis and had a history of at least one nonrenal organ failure or the presence of sepsis. At day 28, the mortality rate was significantly lower in the RAD group than in the CRRT group (33% versus 61%, respectively, $P = 0.08$, χ^2; $P = 0.03$, log-rank (Figure)). The hazard ratio for death in the RAD group compared with the CRRT group was 0.481 (0.23–0.99), adjusting for disease cause. The point estimate for this hazard ratio was similar across subgroups stratified by age, race, and severity of illness. Also, a higher proportion of subjects in the RAD group recovered renal function (53%) as compared with the CRRT group (28%), but this did not reach conventional levels of statistical significance. Although the study is limited by the number of subjects enrolled, no significant safety concerns were raised about the RAD.

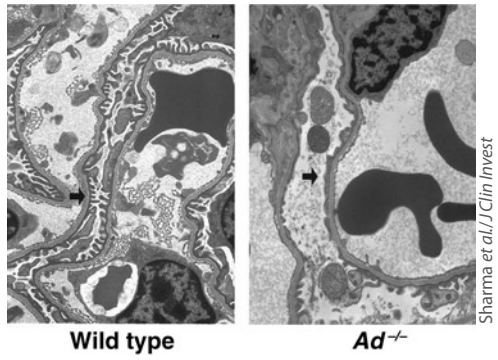
Research to date focusing on the use of dialytic therapies has affected the staggering mortality rate among the critically ill with acute renal failure. Therapies that differ with respect to dialysis dose, frequency or modality, and type of membrane have not demonstrated consistent results. While the safety and feasibility of the RAD will be further explored in subsequent years, this study indicates that the RAD has the potential to impact mortality associated with acute renal failure. (*J Am Soc Nephrol* 2008; **19**: 1034–1040; doi:10.1681/ASN.2007080895)

Lynda Szczech



Kaplan-Meier estimates of survival for patients in the RAD and conventional CRRT groups.

Adiponectin regulates glomerular permeability to albumin



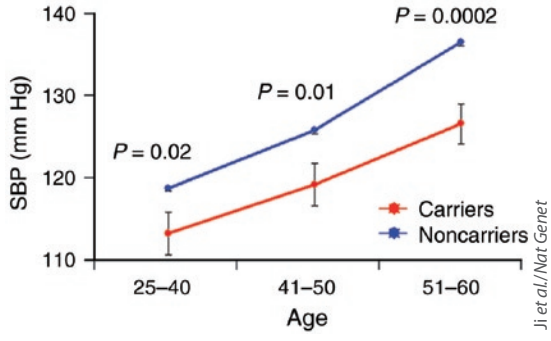
Kidneys of $Ad^{-/-}$ mice exhibit increased podocyte effacement (right) as compared with those of wild-type mice (left). Arrows denote areas of normal foot processes in wild-type mice and areas of foot process effacement in $Ad^{-/-}$.

The hormone adiponectin, a 30-kilodalton protein primarily secreted by adipocytes, circulates in plasma in multimeric forms ranging from trimers to high−molecular weight oligomers containing 12- to 18-mers. It plays an important role in regulating insulin sensitivity, and its plasma level has been recently recognized as a predictive factor for cardiovascular mortality in patients with renal failure. Albuminuria is associated with obesity and diabetes and is a risk factor for cardiovascular and renal disease in these conditions. However, the link between early albuminuria and adiposity remains unclear. In a recent study, Sharma *et al.* used clinical and laboratory work to examine whether adiponectin is a communication signal between adipocytes and the kidney. In a cohort of patients at high risk for diabetes and kidney disease, albuminuria had a negative correlation with plasma adiponectin in obese patients. Remarkably, adiponectin knockout ($Ad^{-/-}$) mice had increased albuminuria and fusion of podocyte foot processes (Figure). Also, when the authors used a fragment of adiponectin that interacts with cellular adiponectin receptors and mimics many of the actions of the full-length hormone, it increased activity of 5′-AMP activated protein kinase (AMPK) in cultured podocytes, and both adiponectin and AMPK activation reduced podocyte permeability to albumin and podocyte dysfunction. These effects appeared to be caused by a reduction in oxidative stress, as adiponectin and AMPK activation both reduced protein levels of the nicotinamide adenine dinucleotide phosphate oxidase Nox4. Finally, $Ad^{-/-}$ mice treated with adiponectin exhibited normalization of albuminuria, improved podocyte

foot process effacement, increased glomerular AMPK activation, and reduced urinary and glomerular markers of oxidant stress. These results suggest that adiponectin is a key regulator of glomerular permeability and that it has an important role in the pathogenesis of albuminuria. (*J Clin Invest* 2008; **118**: 1645–1656; doi:10.1172/JCI32691)
Juan Oliver

Rare mutations in renal salt handling genes contribute to blood pressure variation

Although epidemiologic studies have long since demonstrated the high heritability of variations in blood pressure, identification of the responsible genes has been difficult because of their trait's complexity. Currently, it is unknown even whether common variants or many independent rare mutations account for the contributions of specific genes. Landmark studies of rare mendelian traits carried out mainly in R. Lifton's laboratory identified more than 20 genes in which mutations impart large effects on blood pressure; most of these mutations appear to act by changing net renal salt reabsorption. Several of these disorders, exemplified by Bartter's and Gitelman's syndromes, have recessive traits that lower blood pressure. These observations raise the interesting question of whether the more prevalent heterozygous mutations in these genes might commonly affect the trait. Bartter's syndrome is caused by recessive loss-of-function mutations of the Na-K-2Cl cotransporter gene *SLC12A1* and of the inward rectifier K^+ channel gene *KCNJ1*. Gitelman's syndrome is a less severe salt-wasting disease caused by recessive loss-of-function mutations in the NaCl cotransporter gene *SLC12A3*. The prevalence of Bartter's and Gitelman's syndromes (approximately 1 per million and 1 per 40,000, respectively) suggests that heterozygous disease alleles should be present in at least 1% of the population. In a recent communication, Ji *et al.* reported analysis of these genes in a large, well-characterized cohort. They examined *SLC12A1* (*NKCC2*), *SLC12A3* (*NCCT*), and *KCNJ1* (*ROMK*) in the Framingham Heart Study offspring cohort. This cohort, comprising 5,124 subjects (3,125 for whom DNA samples have been obtained), has been followed for up to 35 years with periodic evaluation of cardiovascular risk factors and other traits, permitting stable assessments of quantitative trait values over time. Using comparative genomics, genetics, and biochemistry, the authors identified subjects with mutations proven or inferred to be functional. These mutations, all heterozygous and rare, produced clinically significant blood pressure reduction and protection from developing hypertension as the subjects aged (Figure). These important findings implicate rare alleles that alter renal salt handling in the variation of blood pressure in the general population, and they show that the carrier state of mutations that inactivate renal sodium transport significantly lowers blood pressure. These findings have serious implications for our understanding of hypertension genetics. (*Nat Genet* 2008; **40**: 592–599; doi:10.1038/ng.118)
Juan Oliver



Heterozygous mutations in *SLC12A3*, *SLC12A1*, and *KCNJ1* lower blood pressure. Systolic blood pressure (SBP) among mutation carriers (red) and noncarriers (blue) at the last examination in different age groups.

Angiotensin II upregulates ACE, downregulates ACE2 via the AT1–ERK/p38 MAP kinase pathway

Approximately 30% of Americans have hypertension, making it one of the most important risk factors for cardiovascular disease and the major cause of mortality in the United States. The recent discovery of the angiotensin II (Ang II)-breakdown enzyme angiotensin I-converting enzyme (ACE) 2 suggests the importance of Ang II degradation in hypertension. Koka *et al.* explored the signaling mechanism by which ACE2 is regulated under hypertensive conditions. Real-time polymerase chain reaction and immunohistochemistry showed that ACE2 mRNA and protein expression levels were high, whereas ACE expression levels were moderate in both the normal kidney and heart. In contrast, patients with hypertension showed ACE upregulation and ACE2 downregulation in both hypertensive cardiopathy and hypertensive nephropathy. The inhibition of ACE2 expression was associated with ACE upregulation and activation of extracellular signal-regulated kinase (ERK) 1/2 and p38 mitogen-activated protein (MAP) kinase. *In vitro*, Ang II upregulated ACE and downregulated ACE2 in human kidney tubular cells, which were blocked by an angiotensin II type (AT) 1 receptor antagonist (losartan) but not by an AT2 receptor blocker (PD123319). Furthermore, blockade of ERK1/2 or p38 MAP kinases by either specific inhibitors or a dominant-negative adenovirus abolished Ang II-induced ACE2 downregulation in human kidney tubular cells. In conclusion, Ang II upregulates ACE and downregulates ACE2 expression levels under hypertensive conditions both *in vivo* and *in vitro*. The AT1 receptor-mediated ERK/p38 MAP kinase signaling pathway may be a key mechanism by which Ang II downregulates ACE2 expression, implicating an imbalance of ACE/ACE2 in hypertensive cardiovascular and renal damage. (*Am J Pathol* 2008; **172**: 1174–1183; doi:10.2353/ajpath.2008.070762)
Marc De Broe